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Winksele, January 4, 2006

Re: International patent application PCT/BE2005/000032
Filing date: 4 March 2005
Applicant: K.U.Leuven Research & Development
Title: "Phosponate nucleosides useful as active ingredients in pharmaceutical compositions for the treatment of viral infections, and intermediates for their production"
Our ref: K3234-PCT/wb/td/kd

To the Written Opinion dated August 30, 2005

Dear Mr. Klein,

The Demand for the above identified patent application has been filed on September 30, 2005.

We herewith file without prejudice a set of amended claims 1-13 in order to overcome the objections made at item V of the Written Opinion. Only claims 1 and 5 have been amended, whereas claims 2-4 and 6-11 remain unchanged. The content and support of amendments into claims 1 and 5 are explained below. New claims 12-13 have been introduced.

Item V

Clarity

With respect to the first objection in this paragraph, we agree with the Examiner that formulae (XXXI) to (XXXVI) cannot fit with the definition of '' O-protected group '' given for " Phos " in claim 5 as originally filed. This is an obvious mistake in formulae (XXXI) to (XXXVI) which is easily and unambiguously remedied by correcting the respective formulas by substituting the " Phos-O " group with the originally intended " Phos " group, with the definition of '' Phos '' being unchanged, except for the following independent correction of error.

In order to remedy another obvious error in the definition of '' Phos " in claim 5 as originally filed, the term " S-protected " should be deleted, since a phosphonothioalkyl group, such as defined for instance on page 9 of the specification, does not include a S-group to be protected. It is obvious to the skilled person that, by analogy with the corresponding phosphonoalkoxy group present in the same definition of '' Phos '', a phosphonothioalkyl group should simply be O-protected. This correction does not introduce subject matter that extends beyond the application as originally filed. It merely constitutes a correction of clerical error which is also consistent, according to the general knowledge of the skilled person, with the use of these compounds (see claim 6) for further processing as an intermediate for making the compounds of claim 1.

With respect to the second objection in this paragraph, we submit that the subject matter of claim 1 is clear as a whole as soon as claim 1 is corrected by introducing the obviously missing notation '' X_2 '' after '' between '' and before '' and '' in the definition of '' n ''. This correction has been made by the Examiner in formulating the lack of clarity objection. We respectfully do not see the type of discrepancy suggested by the Examiner. Formulas II and XIX, for sake of concision, adopt a schematic representation wherein a methylene group is shown, but claim 1 clearly states that said methylene group(s) between P and X^2 ($-P-(C)_n-X^2-$) is/are either unsubstituted (as shown on the schematic representation) or substituted with one or two substituents that are chosen independently from a clearly defined group of substituents.

Novelty

The novelty of the subject matter of claims 1-4 and 6-11 as originally filed has been acknowledged by the Examiner. We respectfully submit that the same conclusion should apply to amended claim 1. We hereby respectfully submit that with the deletion of formula XXVII from claim 5 this claim is novel.

Inventive step

The inventive step of the subject matter of claims 1-4 and 6-11 as originally filed has been acknowledged by the Examiner. We respectfully submit that the same conclusion should apply to amended claim 1.

Although we respectfully disagree with the reasoning about sharing an essential feature with the final inventive compounds for demonstrating an inventive step of their intermediates, for sake of convenience, derivatives of formulas XXVIII to XXX have been removed from claim 5 and are now separately claimed in new claim 12. New claim 13 has been introduced in parallel with claim 6 with respect to using the novel compounds of claim 12 for making the final compounds of claim 1.

Should the Examiner maintain objections to the amended set of claims, we respectfully request the issuance of a second Written Opinion. Thank you.

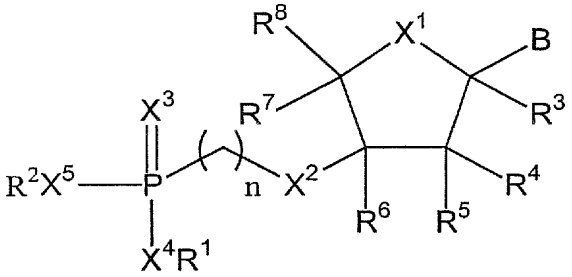
Very truly yours,

William E Bird

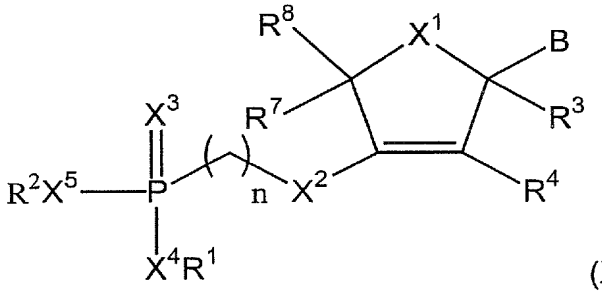
encl.:
- amended claims 1-13, in triplicate (14 pages)

CLAIMS

1. A compound including a heterocyclic nucleobase attached to a first carbon atom of an optionally substituted five-member saturated or mono-unsaturated heterocyclic group selected from tetrahydrofuranyl, tetrahydrothienyl, dihydrofuranyl and dihydrothienyl and further including a phosphonoalkoxy or phosphonothioalkyl group attached to a second carbon atom of said five-member saturated or mono-unsturated heterocyclic group, said first carbon atom being adjacent to the heteroatom of said five-member saturated or mono-unsturated heterocyclic group, and said second carbon atom being adjacent neither to the heteroatom nor to the first carbon atom of said five-member saturated or mono-unsturated heterocyclic group, said compound being represented by one of the general formulae (II) and (XIX):



(II), and



(XIX)

wherein:

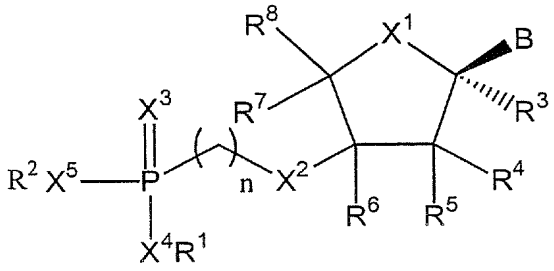
- X^1, X^2, X^3, X^4 and X^5 are each each independently selected from the group consisting of oxygen and sulfur,
- B is a natural or non-natural heterocyclic nucleobase,

- R^1 and R^2 are each independently selected from the group consisting of hydrogen; $(-PO_3R^{16})_m-PO_3R^{17}R^{18}$; alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; aryl; arylalkyl; heterocyclic; heterocyclic-alkyl; acyloxyalkyl; acyloxyalkenyl; acyloxyalkynyl; acyloxyaryl; acyloxyarylalkyl; acyloxyarylalkenyl; acyloxyarylalkynyl; dialkylcarbonate; alkylarylcarbonate; alkylalkenylcarbonate; alkylalkynylcarbonate; alkenylarylcarbonate; alkynyl-arylcarbonate; alkenylalkynylcarbonate; dialkenylcarbonate; dialkynyl-carbonate; wherein said alkyl, alkenyl and alkynyl optionally contains one or more heteroatoms in or at the end of the hydrocarbon chain, said heteroatoms being independently selected from the group consisting of oxygen, sulfur and nitrogen;
- R^3, R^4, R^5, R^6, R^7 and R^8 are each independently selected from the group consisting of hydrogen, azido, halogen, cyano, alkyl, alkenyl, alkynyl, SR^{14} and OR^{14};
- R^{14} is selected from hydrogen; alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; aryl; heterocyclic; arylalkyl; heterocyclic-alkyl; acyloxyalkyl; wherein said alkyl, alkenyl and alkynyl optionally contain one or more heteroatoms in or at the end of the hydrocarbon chain, said heteroatoms being independently selected from the group consisting of oxygen, sulfur and nitrogen;
- R^{16}, R^{17} and R^{18} are independently selected from the group consisting of hydrogen; alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; aryl; arylalkyl; heterocyclic ring; heterocyclic ring-alkyl; acyloxyalkyl; wherein said alkyl, alkenyl and alkynyl optionally contain one or more heteroatoms in or at the end of the hydrocarbon chain, said heteroatoms being independently selected from the group consisting of oxygen, sulfur and nitrogen;
- X^4 and R^1, or X^5 and R^2 may together form an amino-acid residue or polypeptide wherein a carboxyl function of said amino-acid residue being at a distance from the amidate nitrogen not further than 5 atoms is esterified;

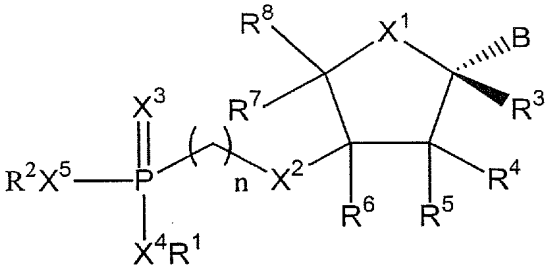
- X^4 and R^1 or X^5 and R^2 may together form a group having the formula – $OC(R^9)_2OC(O)Y(R^{10})_a$ wherein Y = N or O, a = 1 when Y is O and a = 1 or 2 when Y is N;
- R^9 is selected from the group consisting of hydrogen, alkyl, aryl, alkenyl, alkynyl, alkenylaryl, alkynylaryl or alkylaryl, wherein each of said alkyl, alkenyl, alkynyl and aryl groups is optionally substituted with one or more atoms or groups selected from the group consisting of halo, cyano, azido, nitro and OR^{14};
- R^{10} is selected from the group consisting of hydrogen, alkyl, aryl, alkenyl, alkynyl, alkenylaryl, alkynylaryl and alkylaryl, wherein each of said alkyl, alkenyl, alkynyl and aryl groups is optionally substituted with one or more atoms or groups selected from the group consisting of halo, cyano, azido, nitro, OR^{14} and $NR^{11}R^{12}$;
- R^{11} and R^{12} are each independently selected from the group consisting of hydrogen and alkyl, provided that at least one of R^{11} and R^{12} is not hydrogen;
- n is an integer representing the number of methylene groups between X_2 and P, each of said methylene groups being optionally and independently substituted with one or two substituents selected from the group consisting of halogen, hydroxyl, sulhydryl and C_{1-4} alkyl, and n being selected from 1, 2, 3, 4, 5 and 6; and
- m is 0 or 1,

including pharmaceutically acceptable salts, solvates, isomers and prodrugs thereof.

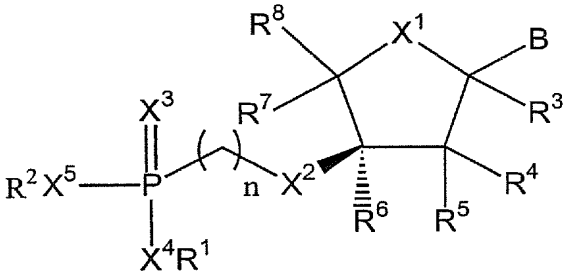
2. A compound according to claim 1, being represented by one of the general formulae (III) to (XVIII):



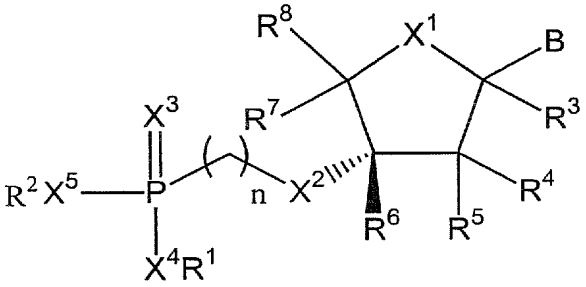
(III),



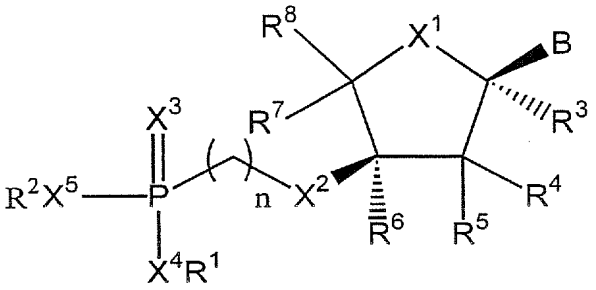
(IV),



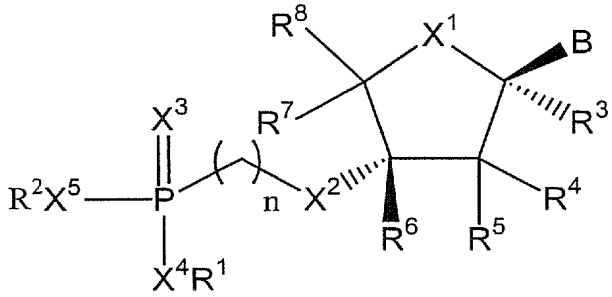
(V),



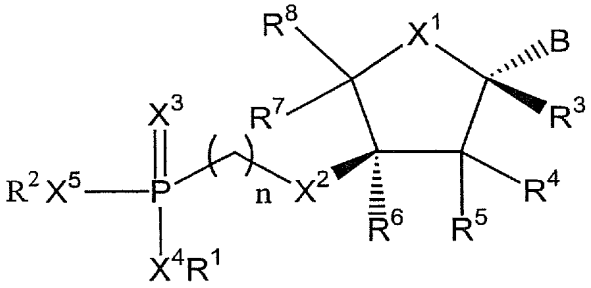
(VI),



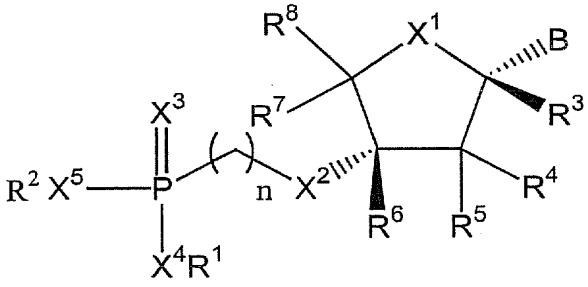
(VII),



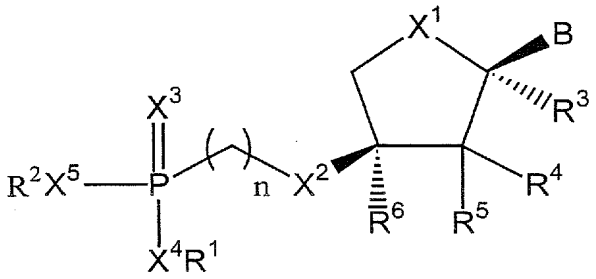
(VIII),



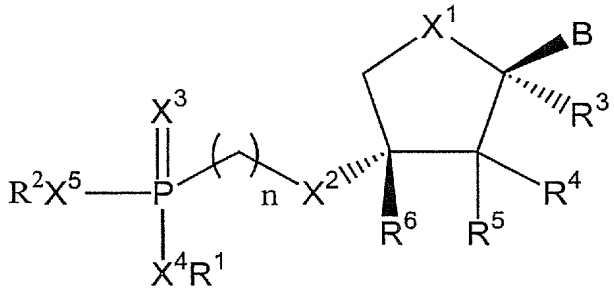
(IX),



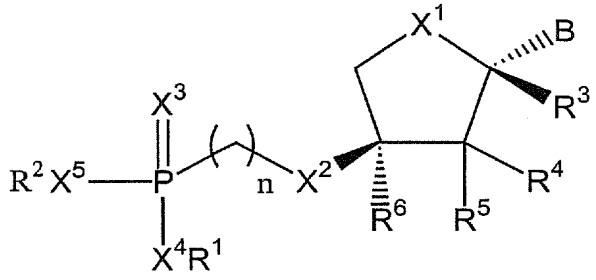
(X),



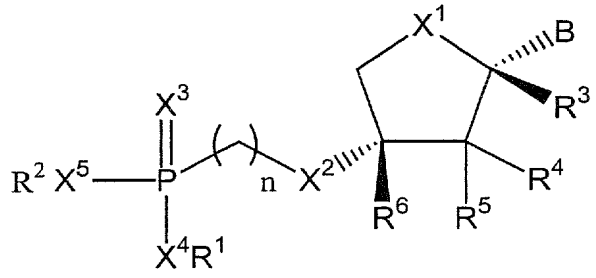
(XI),



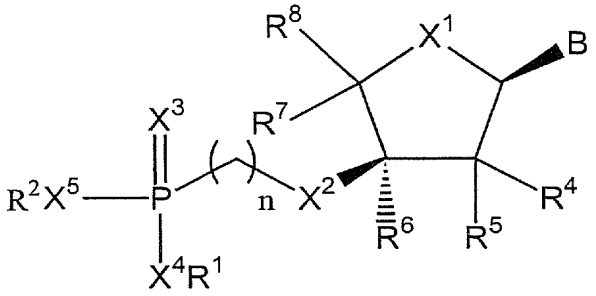
(XII)



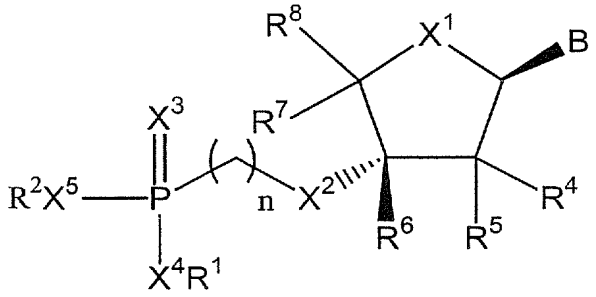
(XIII)



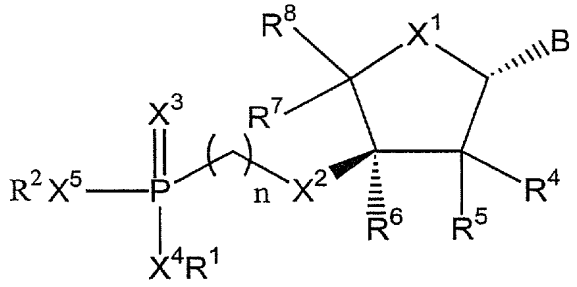
(XIV),



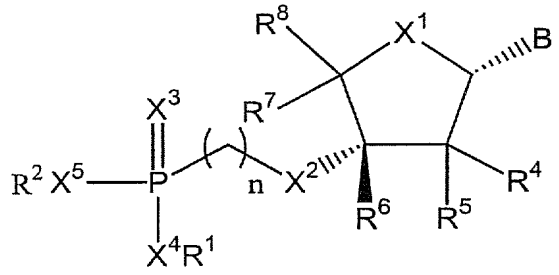
(XV),



(XVI)



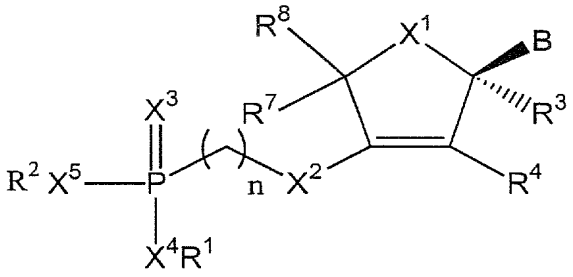
(XVII), and



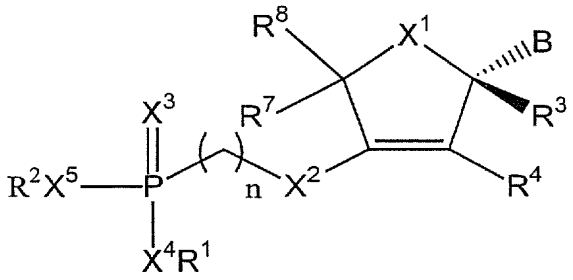
(XVIII)

wherein n, m, B, X^1, X^2, X^3, X^4, X^5, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{14}, R^{16}, R^{17} and R^{18} are defined as in formula (II), including pharmaceutically acceptable salts, solvates, isomers and prodrugs thereof.

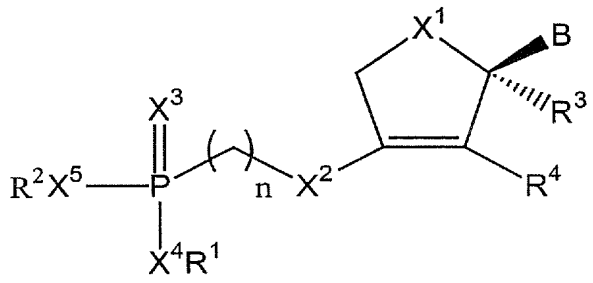
3. A compound according to claim 1, being represented by any of the following formulae (XX) to (XXVI):



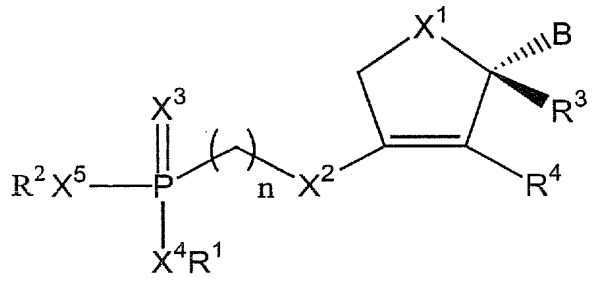
(XX),



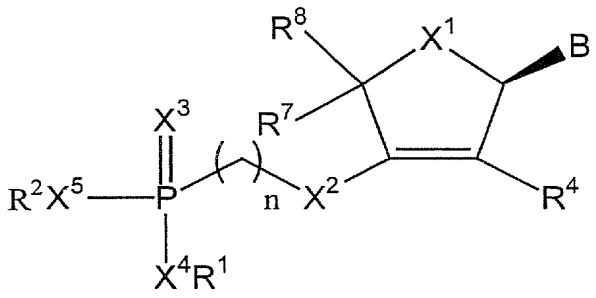
(XXI),



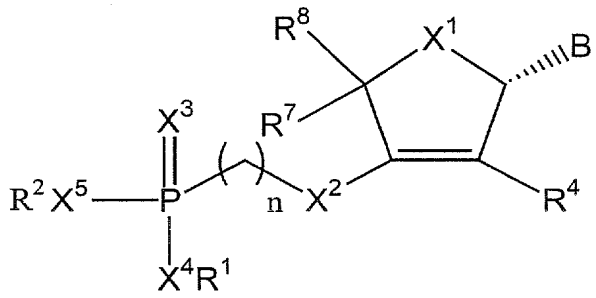
(XXII),



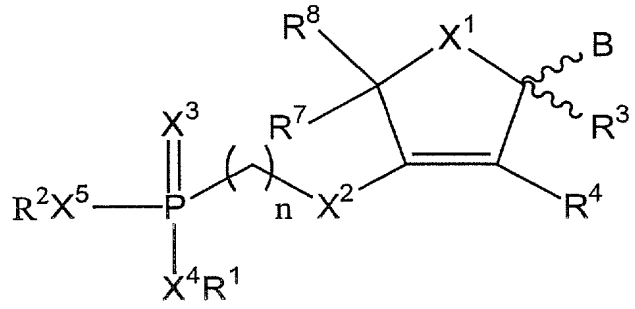
(XXIII),



(XXIV),



(XXV), and



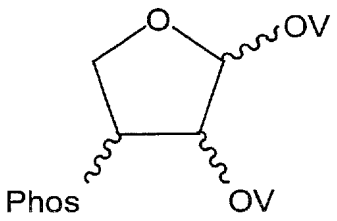
(XXVI),

wherein n, m, B, X^1, X^2, X^3, X^4, X^5, R^1, R^2, R^3, R^4, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{14}, R^{16}, R^{17} and R^{18} are defined as in formula (II), including pharmaceutically acceptable salts, solvates, isomers and prodrugs thereof.

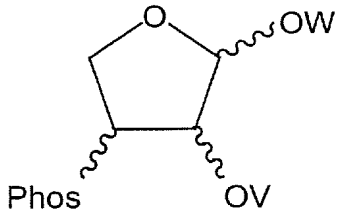
4. A compound according to any of claims 1 to 3, wherein B is selected from the group consisting of hypoxanthine, guanine, adenine, cytosine, inosine, thymine, uracil, xanthine, 8-aza derivatives of 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine;

7-deaza-8-aza derivatives of adenine, guanine, 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 1-deaza derivatives of 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 7-deaza derivatives of 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 3-deaza derivatives of 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 6-azacytosine; 5-fluorocytosine; 5-chlorocytosine; 5-iodocytosine; 5-bromocytosine; 5-methylcytosine; 5-bromovinyluracil; 5-fluorouracil; 5-chlorouracil; 5-iodouracil; 5-bromouracil; 5-trifluoromethyluracil; 5-methoxymethyluracil; 5-ethynyluracil and 5-propynyluracil.

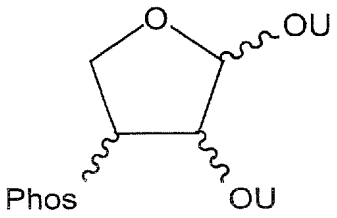
5. A compound represented by one of the following general formulae (XXXI) to (XXXVI):



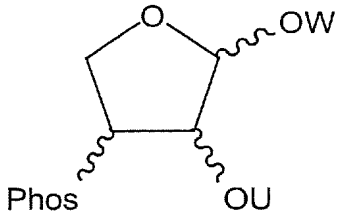
(XXXI),



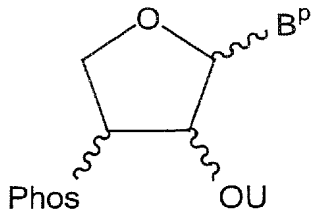
(XXXII),



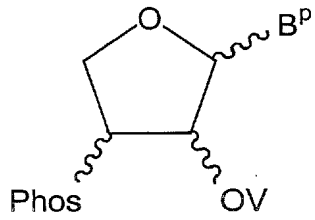
(XXXIII),



(XXXIV),



(XXXV), and



(XXXVI),

wherein:

- U is an acyl group,
- V is a silyl group,
- W is an alkyl group,
- the snake-like symbol means any stereochemical arrangement of the respective bond,
- B^p is an optionally protected heterocyclic nucleobase, and
- Phos is an O-protected phosphonoalkoxy group or phosphonothioalkyl group.

6. Use of a compound according to claim 5 as an intermediate for making a compound according to any of claims 1 to 4.

7. A compound according to any of claims 1 to 4, being selected from the group consisting of :

1-(N^6-benzoyladenin-9-yl)-2-O-benzoyl-3-O-(diisopropylphosphonomethyl)-L-threose (**11**);

1-(thymin-1-yl)-2-O-benzoyl-3-O-(diisopropylphosphonomethyl)-L-threose(**12**);

1-(uracil-1-yl)-2-O-benzoyl-3-O-(diisopropylphosphonomethyl)-L-threose (**13**);

1-(N^4-acetylcytosin-1-yl)-2-O-benzoyl-3-O-(diisopropylphosphonomethyl)-L-threose (**14**);

1-(adenin-9-yl)-3-O-(diisopropylphosphonomethyl)-L-threose (**15**);

1-(thymin-1-yl)-3-O-(diisopropylphosphonomethyl)-L-threose (**16**);

1-(uracil-1-yl)-3-O-(diisopropylphosphonomethyl)-L-threose (**17**);

1-(cytosin-1-yl)-3-O-(diisopropylphosphonomethyl)-L-threose (**18**);

1-(adenin-9-yl)-2-deoxy-3-O-(diisopropylphosphonomethyl)-L-threose (**19**);

1-(thymin-1-yl)-2-deoxy-3-O-(diisopropylphosphonomethyl)-L-threose (**20**);

1-(uracil-1-yl)-2-deoxy-3-O-(diisopropylphosphonomethyl)-L-threose (**21**);

1-(cytosin-1-yl)-2-deoxy-3-O-(diisopropylphosphonomethyl)-L-threose (**22**);

1-(adenin-9-yl)-3-O-(phosphonomethyl)-L-threose sodium salt (**3a**);

1-(thymin-1-yl)-3-O-(phosphonomethyl)-L-threose sodium salt (**3b**);

1-(uracil-1-yl)-3-O-(phosphonomethyl)-L-threose sodium salt (**3c**);

1-(cytosin-1-yl)-3-O-(phosphonomethyl)-L-threose sodium salt (**3d**);

1-(adenin-1-yl)-2-deoxy-3-O-(phosphonomethyl)-L-threose sodium salt (**3e**);

1-(thymin-1-yl)-2-deoxy-3-O-(phosphonomethyl)-L-threose sodium salt (**3f**);

1-(uracil-1-yl)-2-deoxy-3-O-(phosphonomethyl)-L-threose sodium salt (**3g**);

1-(cytidin-1-yl)-2-deoxy-3-O-(phosphonomethyl)-L-threose sodium salt (**3h**);

a pharmaceutically acceptable salt , an isomer, a solvate or a pro-drug thereof.

7. The use of a compound according to any of the claims 1 to 4, for the manufacture of a medicament for the prevention or treatment of a viral infection in a mammal.

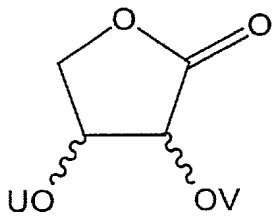
8. The use according to claim 7, wherein said viral infection is an infection by the Human Immunodeficiency Virus (HIV).

9. A pharmaceutical composition comprising a compound according to any of the claims 1 to 4 as an active ingredient in admixture with at least a pharmaceutically acceptable carrier.

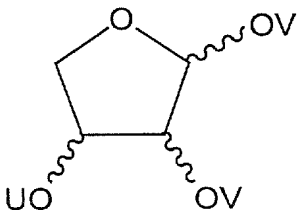
10. A pharmaceutical composition according to claim 9, further comprising an antiviral agent.

11. A method of treatment or prevention of a viral infection in a mammal, comprising administering to the mammal in need of such treatment a therapeutically effective amount of a compound according to any of claims 1 to 4.

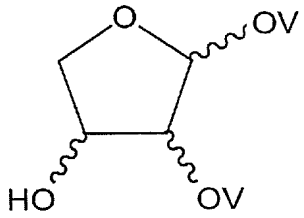
12. A compound represented by one of the following general formulae (XXVIII) to (XXX):



(XXVIII),



(XXIX), and



(XXX),

wherein:

- U is an acyl group,
- V is a silyl group, and
- the snake-like symbol means any stereochemical arrangement of the respective bond.

13. Use of a compound according to claim 12 as an intermediate for making a compound according to any of claims 1 to 4.